In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: January 23, 2024

GUY IRWIN,	*	
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Petitioner,	*	No. 16-1454V
	*	
v.	*	Special Master Gowen
	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
	*	
Respondent.	*	

Renee J. Gentry, The Law Office of Renee J. Gentry, Washington, D.C., for petitioner.
Adam N. Muffett, U.S. Department of Justice, Washington, D.C., for respondent.

RULING ON ENTITLEMENT[1]

On November 4, 2016, Guy Irwin ("petitioner") filed a petition for compensation under the National Vaccine Injury Compensation Program.[2] Petition (ECF No. 1). Petitioner alleges that as a result of receiving an influenza vaccine on November 7, 2014, he suffered a stroke and its sequelae. Petition (ECF No. 1). After a review of the record and an entitlement hearing, petitioner has established by preponderant evidence that he is entitled to compensation.

I. Procedural History

Petitioner filed his claim for compensation on November 4, 2016. Petition. Petitioner filed medical records to support his claim on January 4, 2017. Petitioner ("Pet.") Exhibits ("Exs.") 1-12) (ECF Nos. 6 & 7). Petitioner continued to file additional medical records in 2017 and 2018. *See* Pet. Exs. 13-23.

[1] Pursuant to the E-Government Act of 2002, see 44 U.S.C. § 3501 note (2012), **because this opinion contains a reasoned explanation for the action in this case, I intend to post it on the website of the United States Court of Federal Claims.** The Court's website is at http://www.uscfc.uscourts.gov/aggregator/sources/7. Before the opinion is posted on the Court's website, each party has 14 days to file a motion requesting redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). An objecting party must provide the Court with a proposed redacted version of the opinion. *Id.* **If neither party files a motion for redaction within 14 days, the opinion will be posted on the Court's website without any changes.** *Id.*

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to 34 (2012) (hereinafter "Vaccine Act" or "the Act"). Hereinafter, individual section references will be to 42 U.S.C. § 300aa of the Act.

On April 10, 2019, petitioner filed an expert report from Carlo Tornatore, M.D.[3] and supporting medical literature. Pet. Exs. 24-27 (ECF Nos. 46 & 47). On January 13, 2020, respondent filed a Rule 4(c) report recommending against compensation. Respondent ("Resp.") Report ("Rept.") (ECF No. 62). Respondent also filed an expert report from Steven Messé, M.D.[4] and accompanying medical literature. Resp. Exs. A (ECF Nos. 63-65).

I held a Rule 5 status conference on October 6, 2020. During the status conference, I explained that petitioner's expert, Dr. Tornatore, had proposed a medically plausible theory of vaccine causation, however, there was also litigative risk for petitioner as well. Rule 5 Order (ECF No. 74). I recommended that the case be resolved in ADR. The parties were unsuccessful in resolving the case in ADR. *See* Order Concluding ADR Proceedings (ECF No. 85).

Petitioner filed a supplemental expert report from Dr. Tornatore on October 27, 2021. Pet. Ex. 48 (ECF No. 89). On November 10, 2021, the parties filed a joint status report requesting that an entitlement hearing be set. Joint Status Rept. (ECF No. 90). Respondent filed a supplemental expert report from Dr. Messé and a report from Steven Hedrick, M.D.[5] on February 9, 2022. Resp. Ex. B & C (ECF No. 93).

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[3] Dr. Carlo Tornatore is a Professor and Chair of the Department of Neurology at Georgetown University Medica Center. Pet. Ex. 25. Dr. Tornatore received his undergraduate degree at Cornell University in 1981 and received his medical degree from Georgetown University in 1986. *Id.* at 2. He did a Residency in Neurology at Georgetown University Hospital, followed by a Fellowship in Molecular Virology at the National Institute of Neurological Disorders and Stroke at the National Institute of Heath. *Id.* Following his fellowship, Dr. Tornatore joined the faculty at Georgetown University Medica Center and he has been the Director of Multiple Sclerosis Center for 18 years. *Id.*; Pet. Post-Hearing Brief at 16. The MS Center is involved in 23 clinical trials for treatment of various forms of MS and have been involved in over 62 clinical trials over the past 20 years. Pet. Post-Hearing Brief at 16. Dr. Tornatore is an ad hoc reviewer for the Annals of Neurology, Neurology, Medical Virology, the Journal of Neurovirology, and Gene. Pet. Ex. 25 at 7. Dr. Tornatore has been the lead author on multiple medical articles that focus on the intersection of the immune responses to viruses and the brain. *Id.* at 9-15. Further, Dr. Tornatore has treated patients with different neurological disease, including neuromyelitis optica, transverse myelitis, nervous system vasculitis, and stroke patients. Tr. 6-7; Pet. Post-Hearing Brief at 16. Dr. Tornatore was admitted as an expert in neurology and immunology. Tr. 13.

[4] Dr. Steve Messé is currently an Associate Professor of Neurology at the Hospital of the University of Pennsylvania, School of Medicine. Resp. Ex. B at 1. He received his undergraduate degree from Yale University in 1993 and he graduated from the University of Michigan School of Medicine in 1998. *Id.* Dr. Messé did his residency at the Hospital of the University of Pennsylvania. *Id.* He is board certified in Psychiatry and Neurology, as well as in Vascular Neurology. *Id.* Dr. Messé serves as an ad hoc reviewer for many publications, including the Nature Clinical Practice Neurology, European Journal of Neurology, Journal of Neuroimaging, and Cardiovascular Therapeutics. *Id.* at 2. Dr. Messé has been the lead author or co-authored numerous medical articles that discuss neurology and cardiology. *Id.* at 8-25. Dr. Messé does clinical work at the Hospital at the University of Pennsylvania which focuses primarily on stroke patients. Tr. 98. Dr. Messé was admitted as an expert in neurology and vascular neurology. Tr. 102.

[5] Dr. Stephen Hedrick is currently an emeritus professor at the University of California San Diego, CA. Tr. 54; Resp. Ex. E at 1. He received his undergraduate degree from the University of California and his Ph.D. in molecular biology and biochemistry from the University of California in Irvine, California. Resp. Ex. E at 1. Dr. Hedrick did his post-doctoral fellowship at the Laboratory of Immunology at the National Institute of Health. *Id.* Following his fellowship, he began working at the University of California in San Diego, CA in the Department of Biology. *Id.*; Tr. 55. Dr. Hedrick became the Department Chairman for the Department of Biology for seven years. Tr. 55. Dr.

On May 12, 2022, an entitlement hearing was held, where Dr. Carlo Tornatore testified for petitioner and Drs. Steven Messé and Stephen Hedrick testified on behalf of respondent. Both parties filed post-hearing briefs. Pet. Post-Hearing Brief ("Pet. Brief") (ECF No. 110); Resp. Post-Hearing Brief ("Resp. Brief") (ECF No. 111). This matter is now ripe for adjudication.

II. Evidence Submitted

a. Summary of petitioner's medical history

Petitioner, who was 62 years old at the time, received the flu vaccine on November 7, 2014 at a CVS pharmacy in Leesport, Pennsylvania. Pet. Ex. 1. Petitioner stated that he felt ill on the evening of November 7, 2014, and went to bed early. Pet. Affidavit ("Aff.") ¶ 7. The following day, Saturday, November 8, 2014, petitioner and his wife travelled to Philadelphia, Pennsylvania to see family. *Id.* ¶ 8. Petitioner stated that he had an upset stomach and he was irritable. *Id.* at ¶ 7. Petitioner's wife had to complete the drive to Philadelphia and drive the entire way home because he felt so ill. Petitioner stated that during the visit with family, he "slept on the sofa during almost all the visit." *Id.* at ¶ 8. He stated that his irritability continued during the car ride home and he went to bed immediately when they got home. *Id.*

On Sunday, November 9, 2014, petitioner went to church, where he was the Building and Grounds Manager, to help prepare for the Sunday services. Pet. Aff. ¶ 9-10. He stated that between the first and second service of the morning, he began to feel strange and had difficulty controlling his movements and keeping his balance. *Id.* A registered nurse who was a parishioner recognized the symptoms of a stroke and called an ambulance to the church at approximately 10:00 AM. Pet. Ex. 6 at 3. According to the ambulance report, petitioner reported, "The pressure in my head is too high," and he had developed pain on the front left side of his head. *Id.* Petitioner was transported to Reading Hospital Medical Center. *Id.*; *see also* Pet. Ex. 10 at 11.

In the emergency department of the Reading Hospital Medical Center, petitioner reported headache, dizziness and visual changes. Pet. Ex. 10 at 11. Petitioner reported that he was ill "yesterday" and "attributed" it to the flu shot he had received on Friday. *Id.* Around 10:00 AM, petitioner began to have a headache on the left side [of his head] with some visual changes, in the right lower visual field and some decreased vision in the periphery. *Id.* During his neurological exam, petitioner was unable to recount the month and "unable to name a pen." *Id.* at 13. Petitioner was admitted for further evaluation for a stroke. *Id.* at 15.

Dr. Ian Goonewardene evaluated petitioner upon admission on November 9, 2014. Pet. Ex. 10 at 16. He noted that petitioner had a NIH stroke scale of 6.[6] *Id.* Dr. Goonewardene

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Hedrick has authored or co-authored numerous articles about immunology, but specifically about T-cells. Resp. Ex. E at 2-11. Dr. Hedrick was admitted as an expert in immunology. Tr. 58.

[6] The NIH Stroke Scale is a validated, standardized neurologic assessment providing a measure of stroke severity with scores ranging from zero (normal) to 38 (coma). A score less than 5 is considered a mild stroke. 6 is

assessed petitioner with "acute ischemic stroke." *Id.* at 18. He wrote, "The onset was sudden and associated with true visual field deficits." *Id.* Petitioner had an MRI the same day which showed, "Moderate sized, acute infarct involving the posterior medial temporal lobe, and occipital lobe on the left. A small component of the infarct involves the posterolateral left thalamus." Pet. Ex. 4 at 19.

Petitioner was evaluated by neurologist Dr. Karen Hoerst. Pet. Ex. 10 at 35. During this evaluation, petitioner reported "concern that he received [the] flu shot on Friday and is concerned that his stroke is related to this." *Id.* The physical exam revealed a right homonymous hemianopia. *Id.* at 37. Dr. Hoerst recommended that petitioner have a cardiology evaluation, including a transthoracic echocardiogram to look for the source of the thrombus. *Id.* at 38.

Petitioner was discharged on November 12, 2014. Pet. Ex. 10 at 3. His discharge diagnoses were hypertension, acute left PCA stroke, and hyperlipidemia. *Id.* Petitioner was discharged to the Reading Hospital rehabilitation facility. *Id.* at 4. He was in the rehabilitation facility until November 20, 2023.

Petitioner had a consult with cardiologist, Dr. William Finneran on December 15, 2014. Pet. Ex. 5 at 4. At this appointment, petitioner was being evaluated for a "loop recorder due to [his] recent left occipital CVA with PCA infarct accompanied by right-sided weakness and expressive aphasia, as well as visual field cut." *Id.* Petitioner did not have any chest pain or shortness of breath. Dr. Finneran wrote that petitioner was "post-Holter monitor on 12/01/2014 which showed over 1000 PACs (premature atrial contractions) with 5 atrial pairs with one 4-beat run of ventricular tachycardia and 577 PVCs (premature ventricular contractions)." *Id.* at 5. Further, petitioner reported that "he had a flu shot the day before his stroke," and that "he is not convinced that his stroke was not from this flu shot." *Id.* Petitioner declined the loop recorder at that time.

On January 19, 2015, petitioner had a follow-up appointment with neurologist, Dr. Hoerst. Pet. Ex. 9 at 4. At this appointment, Dr. Hoerst wrote, "The patient reported that he was in his usual state of health until approximately 2 days prior to the stroke when he received his flu shot, then began to feel ill for approximately 2 days and then his wife noticed a significant change in his personality the day prior to coming into the hospital. On arrival to the hospital a plain head CT showed mild edema in the left occipital lobe and he was not given IV tPA due to his CT findings and duration of symptoms….MRI showed a left PCA infarct with evidence of a left P2 cut off." *Id.* Further, Dr. Hoerst recommended that petitioner undergo an evaluation by cardiology for placement of an implantable loop recorder to look for underlying occult atrial fibrillation. *Id.* Dr. Hoerst assessed petitioner with "left PCA infarct of unclear etiology," and wanted to evaluate petitioner for "other etiologies of stroke." *Id.* at 6. Petitioner did not want to have additional workup.

On March 27, 2015, petitioner had another appointment with cardiologist, Dr. Finneran. Pet. Ex. 5 at 7. Dr. Finneran wrote that petitioner "presents today to discuss loop recorder

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moderated. Resp. Ex. A at 2; Petitioner's score in the emergency room was separately recorded as 3. Pet. Ex .6 at 13, 6.

implantation to evaluate for his palpitations and possible paroxysmal atrial fibrillation." *Id.* Further, Dr. Finneran stated that petition was "without further complaints of stroke or TIA symptoms but has now decided to go forward with loop recorder implantation." *Id.* Under petitioner's "Past Cardiac, Medical and Surgical History," it was recorded that petitioner had "(1) left occipital CVA with posterior cerebral artery infarct on 11/09/2014; (2) hypertension; (3) hyperlipidemia; (3) PACs, paroxysmal atrial tachycardia, nonsignificant ventricular tachycardia on Holter monitor 12/01/2014." *Id.* Petitioner had an EKG which showed "normal sinus rhythm, normal EKG, and nonspecific ST wave changes." *Id.* at 8. Petitioner opted to have a loop recorder implantation, which occurred on April 10, 2015.

On August 22, 2015, petitioner was taken to the emergency department at the Reading Hospital when he was found unresponsive by his wife. Pet. Ex. 10 at 168. The record states that petitioner was "found by wife on floor with snoring respirations. No signs of trauma. [Patient] vomiting upon arrival. [Patient] is nonverbal, not responding. History of CVA." *Id.* His Glasgow Coma Scale score was 7.

At a follow-up appointment with Dr. Finneran on October 15, 2015, petitioner reported that he had been hospitalized for a seizure in August 2015. Pet. Ex. 5 at 9. He had been experiencing some visual field cuts, from approximately 12:00 pm to 3:00 pm. *Id.* Petitioner had an in-office ECG which showed "sinus bradycardia with a rate of 59 beats per minute." *Id.* at 10. Additionally, Dr. Finneran reviewed petitioner's loop recorder which showed "three symptom episodes and one tachycardia episode….The first symptom episode was a single PAC. The second symptom episode showed two single PACs and the third was negative for arrhythmia or extra beats." *Id.* Under "Impression/Plan," Dr. Finneran wrote, "(1) Cryptogenic stroke post-loop recorder with no evidence of arrythmias. He was originally maintained on a full-dose aspirin. He had a recent DVT and PE. We will have him drop his aspirin down to 81 mg now that he is fully anticoagulated on Coumadin." *Id.*

Petitioner had a follow-up appointment with Dr. Finneran on October 20, 2016. Pet. Ex. 30 at 6-7. Dr. Finneran wrote that petitioner has been without complaints of repeat stroke or TIA symptoms and that he had been on Coumadin until September 2016. *Id.* at 6. Petitioner's loop recorder had one episode of atrial fibrillation lasting for 36 hours on September 2, 2016, but petitioner was asymptomatic. *Id.* Dr. Finneran performed an ECG in the office which showed normal sinus rhythm at a heartrate of 71. *Id.* Petitioner was diagnosed with "left occipital cerebrovascular accident with posterior cerebral artery infarct with left-sided weakness with mild expressive aphasia Nov. 9, 2014, hypertension, hyperlipidemia, history of deep vein thrombosis and pulmonary embolus for which petitioner completed one year of Coumadin therapy, and suspected sleep apnea. *Id.* It was recommended that petitioner continue Coumadin for stroke prophylaxis, and he was encouraged to diet and exercise. *Id.*

Petitioner continued to regularly have check-ups for various conditions, including a sunburn and acute sinusitis. *See generally* Pet. Ex. 29. On April 25, 2019, petitioner had a follow-up with his primary care physician to review his chronic medical conditions and labs results. Pet. Ex. 29 at 80. It was noted that petitioner's sleep study showed that he had "severe sleep apnea" but that he refused to wear CPAP. *Id.* The record also noted that petitioner had

"stable chronic medical problems" and that he was using aspirin and Coumadin. *Id.* Petitioner was asked to follow-up in three months. These are the most up-to-date records.

b. Petitioner's expert's opinion on vaccine causation

Petitioner's expert, Dr. Carlo Tornatore, opined that the flu vaccine petitioner received on November 7, 2014 was the cause of petitioner's ischemic stroke that occurred on November 9, 2014. Pet. Ex. 24 at 6. Dr. Tornatore opined that the influenza vaccine induces "an inflammatory response with a subsequent pro-thrombotic state," which can result in an acute cerebral ischemic event. *Id.*

During the hearing, Dr. Tornatore testified that the influenza vaccine is intended to induce an inflammatory response. Tr. 15. The immune response to the influenza vaccine, "via cytokines, chemokines, or even cellular elements…led to an inflammation of the endothelium or the inside of a blood vessel and that caused a blood clot to form which stopped the blood flow to the…brain and caused an ischemic event." Tr. 16. In other words, "there was an inflammatory response to the vaccine that resulted in a clot to form in a blood vessel." *Id.* In his opinion, the onset of petitioner's symptoms beginning 24-hours after vaccination is an appropriate timeframe for an inflammatory response to lead to a pro-thrombotic state. Pet. Ex. 24 at 7.

Dr. Tornatore referenced a case report by Thoon, which described a 10-year-old girl who developed a stroke one day after receiving a flu vaccine. Pet. Ex. 26.[7] The case report explains that the child presented to the hospital with "acute-onset vertiginous giddiness, blurred vision, headache, and non-bilious vomiting," that began six-hours prior to admission. *Id.* at 2. The child did not have any hearing loss, focal numbness or weakness and there was no history of head trauma, but she did receive an influenza vaccine the day before the symptoms began. *Id.* The authors of Thoon noted that a "review of literature revealed two recent reports of stroke temporally associated with influenza vaccination in adults; however, both reported cases had underlying co-morbidities that substantially increased their predisposition to developing a stroke." *Id.* at 3. In the Thoon case, no underlying prothrombotic or autoimmune conditions were found. *Id.* Dr. Tornatore acknowledged that the authors of Thoon were "careful to say that [they] were not a hundred percent sure that [the flu vaccine and the stroke] were related to the vaccine. But stroke in the young is exceedingly rare, and to have that very striking temporal relation of vaccination and then an infarct in the posterior circulation, not unlike the same distribution that [petitioner] had is unusual." Tr. 17.

Dr. Tornatore referenced another case report by Lin et al., which described a 75-year-old man who suffered a posterior circulation ischemia after receiving an influenza-A vaccination. Pet. Ex. 27.[8] The patient in this case report received an influenza vaccine at 10:00 AM, went home and took a nap from noon until 5:00 pm. *Id.* The patient woke up with dizziness, asthenia,

[7] Thoon, K. et al., *Childhood Stroke After Influenza Vaccination,* 21 Proc. of Sing. Healthcare 298 (2012). [Pet. Ex. 50].

[8] Lin, Yi-Pin et al., *Ischaemic stroke and influenza A H1N1 vaccination: a case report,* 7(2) Arch Med Sci, 345-348 (2011). [Pet. Ex. 27].

(weakness) unsteady gait with deviation on the left side, and the inability to hold objects by hand properly. *Id.* at 2. These symptoms subsided thirty minutes later but occurred three or four times daily for approximately seven days before the patient presented to the hospital. *Id.* An MRI showed "high DWI and low ADC intensities scattered in the left cerebellum compatible with infarctions within the vascular territory of the posterior inferior cerebella artery." *Id.* Lin explained that "Our patient's infarction is compatible with small-to-medium size artery occlusion which is also seen in other ischaemic stroke patients after vaccination." *Id.* The authors also reviewed VAERS data and found that, "the leading vaccine reported to be complicated with ischaemic stroke is seasonal flu, followed by hepatitis A and B virus, pneumococcus, diphtheria/pertussis/tetanus toxoid, poliomyelitis, and *Haemophilus influenzae.*" *Id.* They found that 164 individuals reported ischaemic stroke after receiving the seasonal flu vaccine and 18 after the influenza A/H1N1 vaccine. *Id.* The authors explained that in these patients, "…ischaemic stroke occurs within the first day in 22% and 18% of subjects receiving vaccination with influenza A/H1N1 and seasonal flu vaccine, respectively." *Id.* Furthermore, the authors wrote:

> Vaccination can induce inflammatory and immunological responses. A flare-up of lupus has been reported. A generation of temporary inflammatory reactions with an elevation of cytokines after vaccination with *Salmonella typhi* vaccine, increase of blood antiphospholipid antibodies with influenza vaccine, and vasculitis with a couple of vaccines have been identified. In our patient, we did not detect an abnormal alteration of immune and coagulation function or angiopathy, but that does not completely exclude their participation.

Id. at 4; Tr. 21.

Lin also observed that "nearly half of ischaemic stroke children have concomitant stroke risk factors, such as cardiac disease, autoimmunity disorders, vasculopathy, or coagulopathy," which led the authors to opine that "vaccination may promote a pre-existing prothrombotic condition," and that "vaccination should be carefully evaluated and monitored in individuals associated with old age or stroke risk factors." *Id.* at 4; *see also* Tr. 21-22. Dr. Tornatore stated that the authors of Lin recognized the same "biological mechanism….that an inflammatory cascade could have been the etiology of the infarct," that occurred in this case. Tr. 21.

Dr. Tornatore stated that an immune stimulus, such as vaccination, can stimulate the coagulation system and/or impair the endothelial-dependent dilation of blood vessels in the brain. Tr. 21; *see also* Pet. Ex. 48 at 2. He referenced an article by Hingorani et al, which explored how endothelial dysfunction "underlies the association between an acute inflammatory episode and the transiently increased risk of a cardiovascular event by examining the effects of an experimental inflammatory stimulus on endothelium-dependent vasodilation." Pet. Ex. 49.[9] In Hingorani, the authors vaccinated subjects with the *salmonella typhi* vaccine to "initiate a systemic inflammatory response." *Id.* at 3. The authors found that the "plasma concentration of the proinflammatory cytokine IL-6 increased." *Id.* Additionally, the authors explained:

[9] Hingorani, A. et al., *Acute Systemic Inflammation Impairs Endothelium-Dependent Dilation in Humans,* 102 Circulation, 994-99 (2002). [Pet. Ex. 49].

> ….in relation to cardiovascular risk, the elevation of IL-6 is of particular interest because IL-6 is presumed to be an important, if not the principal, stimulus to the synthesis of C-reactive protein, and elevated C-reactive protein seems to be predictive of risk of cardiovascular events.

Id. at 3.

They found that the "mild systemic inflammatory response," to the vaccine, "was associated with profound, but temporary suspension of endothelium-dependent relaxation." *Id.* Hingorani stated that, "These findings demonstrate that even a relatively mild systemic inflammatory response is associated with significant alteration in the endothelial function of a type commonly thought to be associated with increased cardiovascular risk." *Id.*

Dr. Tornatore observed that in the Hingorani study, "blood vessel dilation was depressed," as early as eight hours after vaccination, but returned to normal by 32-hours post-vaccination. Pet. Ex. 48 at 2. He explained that in Hingorani, the authors used the vaccine as a model to study inflammation in cardiovascular disease, not study infection level. Tr. 23. Instead, according to Dr. Tornatore, the authors were using "a vaccine model as a proxy to look at inflammation," because it can recapitulate what we see with infection. *Id.* In his report, he stated, "Hingorani and colleagues did…feel that the post-vaccinal endothelial dysregulation 'might explain the association between infection and inflammation and the enhanced risk of an acute cardiovascular event.' " Pet. Ex. 48 at 2. He testified that the vaccine model as demonstrated by Hingorani provides a valid model to show what happens in infection and vaccination and that the mechanism is the same in terms of increasing cardiovascular risk. Tr. 23-24. Further, he explained that not only does Hingorni validate the vaccine model, but that the mechanisms for how the inflammatory process can change the vascular tree by either vaccination or infection are comparable. *Id.* He explained that in an individual, such as the petitioner, who may have pre-existing factors for vascular disease, such as hypertension, the wall of the vascular tree may have atherosclerotic luminal narrowing and diminished vasoreactivity, putting the individual at further risk for a vascular occlusion "by virtue of a narrowed lumen of the vessel." Tr. 25.

Dr. Tornatore stated that petitioner's medical records demonstrated that he began to have systemic symptoms almost immediately after receiving the flu vaccine. Tr. 26. He observed that petitioner's admission history notes that petitioner had "generalized malaise and irritability," for the two-days after he received the flu vaccination. Tr. 26; *see also* Pet. Ex. 10 at 6. Dr. Tornatore explained that generalized malaise is a systemic response that is caused by the elevation in proinflammatory cytokines in response in this case to the flu vaccine. Pet. Ex. 48 at 2; Tr. 29. Dr. Tornatore referenced the article by Christian et al., which explored the relationship between subjective side effects and serum proinflammatory cytokines after vaccination. Pet. Ex. 50.[10] The authors vaccinated subjects with the trivalent flu vaccine and then measured proinflammatory cytokines in the subjects and the subjective side effects. *Id.* at 1. The authors found that subjects who reported systemic symptoms, such as headaches, nausea, tiredness or

[10] Christian et al., *Proinflammatory cytokine responses correspond with subjective side effects after influenza virus vaccination,* 33 Vaccine 3360-3366 (2015). [Pet. Ex. 50].

mild achiness, had marginally higher IL-6 cytokine levels compared to baseline. *Id.* at 6. Additionally, they found that TNF-α was elevated one-day post-vaccination in patients that reported systemic symptoms. *Id.* at 5. Further, the authors found that MIF, another pro-inflammatory cytokine was elevated in the subjects that reported systemic symptoms two days post-vaccination. *Id.* Dr. Tornatore explained that the Christian article demonstrates that systemic symptoms correlated with elevations of pro-inflammatory cytokines. Tr. 29; *see also* Pet. Ex. 48 at 2. R.

Dr. Tornatore stated that both the Hingorani and Christian articles when read together showed that "cytokine and chemokine networks are stimulated [following vaccination] and that they then impair endothelial dilation or just affect the vascular tree." Tr. 29; Pet. Ex. 48 at 2. He testified that the authors of Hingorani noted that vaccination can cause inflammation and that inflammation "increases the risk of a cardiovascular event." Tr. 30. Dr. Tornatore stated that the vaccine can cause endothelial dysregulation which "may explain the association between infection and inflammation and the enhanced risk of an acute cardiovascular event." Tr. 30. He further explained how in a susceptible individual with pre-existing vascular disease could be more at-risk of a thrombotic stroke, stating:

> …because if somebody has underlying vascular disease, the inner lining of their blood vessel is not normal. They probably have some degree of atherosclerotic disease. There's already some embedded inflammation in the wall of the blood vessel…and then you add another inflammatory event on top of that with maybe some narrowing of the blood vessel, and then you'll get a thrombus formation in the situ.

Tr. 30.

Dr. Tornatore, responding to Dr. Hendrick's contention that the flu vaccine does not trigger a sufficient inflammatory event to result in a thrombotic event, acknowledged that cytokine and chemokine levels after vaccination may not be as high as after a wild-type infection, however, they present in a "comparable pattern." Tr. 33. He asserted that both wild infection and vaccination result in cytokine stimulation. *Id.* Dr. Tornatore argued that the Talaat et al. paper, submitted by respondent, demonstrated that inflammatory cytokines are triggered rapidly by the flu vaccine. Tr. 33; *see* Resp. Ex. C, Tab 10.[11] The authors studied serum cytokine and chemokine changes after administration of the influenza vaccine and found that IFN-γ and IP-10 were significantly elevated beginning 7 hours post-vaccination and remained elevated 44 hours after vaccination. Resp. Ex. C, Tab 10 at 6. Further, the authors found that there were "significant differences in median cytokine/chemokine levels…at one or more time points for all of the proinflammatory and chemokine analytes….[h]owever, it was difficult to categorize patterns of change over time for many of the analytes due to considerable interindividual variability." *Id.* at 3-4. Dr. Tornatore observed that the authors of Talaat identified one individual (subject 8) who reported both myalgia and injection site pain post-vaccination, also had a "distinctive, early cytokine response profile which included IL-6, IL-8, IP-10, MCP-1, TNF-α, TARC, and MCP-4." Tr. 34; Resp. Ex. A, Tab 10 at 1, 6. Dr. Tornatore

[11] Talaat, K. et al., *Rapid changes in serum cytokines and chemokines in response to inactivated influenza vaccination*, 12 Influenza and Other Respiratory Viruses, 202-210 (2018) [Resp. Ex. C, Tab 10].

opined that subject 8 was a "super responder, when exposed to the influenza vaccine [and] had a response that was markedly different than the others and had a marked response within 3 to 7 hours." Tr. 35. Talaat explained that Subject 8 of the study not only had a markedly higher proinflammatory response earlier after vaccination, but also had higher antibody response to all three strains of the influenza virus in the vaccine. Resp. Ex. A, Tab 10 at 4. The authors theorized that Subject 8's strong antibody response to the vaccine components suggested a memory response to the vaccine. *Id.* Dr. Tornatore stated that Talaat shows that some individuals can have a proinflammatory response to the vaccine that is comparable to a response generated by the wild-type infection, particularly in individuals who have been previously vaccinated or had an infection. Tr. 37.

In response to respondent's experts' assertion that epidemiological studies, such as the Smeeth et al. article, demonstrate that there is "no increase in the risk of vascular events" after vaccination, Dr. Tornatore explained that such studies may not actually identify rare events because of modeling and the rarity of the event. Tr. 40; *see* Resp. Ex. A, Tab 5.[12] He explained that the Smeeth et al. article is using a statistical model to try to answer the question of whether a rare event can occur and that "the modeling [being used] is not powered to be able to identify the rare event. *Id.* Smeeth et al. studied "the risks of myocardial infarction and stroke after common vaccinations and naturally occurring infections," based off of data provided by the United Kingdom General Practice Research Database. Resp. Ex. A, Tab 5. The authors found that acute lower respiratory tract infections and urinary tract infections are associated with a transient increased risk of a vascular event and that there was "no increase in the event rate after influenza, tetanus, and pneumococcal vaccines." *Id.* at 6. However, finding no increase in the event rate does not mean that no adverse events occurred after vaccination. For example, the authors identified 76 cases of stroke 1-3 days after vaccination, compared to 244 cases of stroke in the same time period after a "systemic respiratory tract infection." *Id.* at 5. These numbers were identified after the authors excluded 12,572 cases of stroke because of "uncertain vaccination dates." *Id.* Dr. Tornatore stated that excluding such a large number of cases could have impacted the outcome of the study, but more importantly, epidemiologic studies cannot exclude the occurrence of a rare event, such as a vaccine-related neurologic injury. Pet. Ex. 48 at 4. He stated that "trying to use an epidemiologic tool to exclude a rare event doesn't make sense from an epistemological standpoint." Tr. 42. Later, Dr. Tornatore testified that "there's always going to be a rare event," and there will be some people, like the patient in the Talaat article that have "a very profound response to the influenza vaccination that others in the cohort did not." Tr. 143.

Dr. Tornatore also explained that the Smeeth article does not show that the vaccine has a protective effect against stroke. Tr. 138. He stated that respondent's experts were misinterpreting the article's findings. *Id.* Dr. Tornatore observed that while Smeeth did not find an increased risk of stroke after vaccination, the "protective effect….may have been due to the administration of vaccination when people were in periods of relatively good health." Tr. 138; Resp. Ex. A, Tab 5 at 7. Dr. Tornatore testified that the authors recognize that "the protective effect was not due to the vaccination itself, but it could have been the behavior," of the patient.

[12] Liam Smeeth, Ph.D. et al., *Risk of Myocardial Infarction and Stroke after Acute Infection or Vaccination,* 351 New Eng. J. Med. 2611-8 (2004). [Resp. Ex. A, Tab 5].

Tr. 140. Further, the "protective effect of the vaccine" is not that the vaccine actually prevents stroke, but it prevents influenza which is a risk factor for stroke. Tr. 142.

Dr. Tornatore asserted that petitioner's clinical presentation of the ischemic stroke occurring two days post-vaccination fits his theory of vaccine causation. Tr. 44. Dr. Tornatore explained that the rapid onset of petitioner's systemic symptoms, such as the headache and malaise, are consistent with a rapid cytokine release. Tr. 45. Dr. Tornatore also associated petitioner's convulsive episode that occurred on August 22, 2015 as "late sequelae" of petitioner's initial stroke. Tr. 43.

He testified that petitioner received the flu vaccine on November 7, 2014 and he began to have systemic symptoms. Tr. 42. Dr. Tornatore observed that such systemic symptoms included headache, generalized malaise, and irritability. Pet. Ex. 24 at 2; *see also* Pet. Ex. 10 at 16. By November 9, 2014, two days after the vaccination, petitioner had visual changes and a localized headache on his left side and his NIH stroke score was a 6. Pet. Ex. 10 at 13. Dr. Tornatore stated that petitioner was diagnosed with an acute ischemic stroke. Tr. 42; Pet. Ex. 10 at 18. Dr. Tornatore acknowledged that a heart loop recorder petitioner had implanted in April 2015, well-after the initial stroke, identified some atrial fibrillation, but at the time of petitioner's stroke, he did not suffer from atrial fibrillation. Tr. 43. On August 22, 2015, petitioner suffered from a convulsive episode which was associated with petitioner's initial stroke. Tr. 43; Pet. Ex. 10 at 156, 168 ("patient suffered seizure activity second to a recent left PCA stroke from November 2014.").

Additionally, Dr. Tornatore explained that petitioner's underlying history of hypertension contributed to his increased risk of a stroke, but it was not the cause of petitioner's stroke on November 7, 2014. Tr. 46. Dr. Tornatore testified that hypertension causes changes in the endothelial walls triggered by inflammation. *Id.* With pre-existing hypertension, petitioner likely had some inflammatory changes in the wall of the vessel[s] in the form of atherosclerotic disease, and then another stimuli, the flu vaccine, led to increased inflammation leading to the thrombus formation. *Id.* Dr. Tornatore recognized that petitioner was "clearly at risk" with pre-existing hypertension, but noted that the case report described in Thoon, where a child developed a stroke after receiving the influenza vaccine demonstrates that this injury can occur "independent of any previous vascular injury." Tr. 46.

Finally, Dr. Tornatore opined that the onset of petitioner's stroke symptoms, occurring within 24-hours of receiving the influenza vaccination was within an appropriate time-period for an inflammatory response to lead to a pro-thrombotic state. Pet. Ex. 24 at 7; Tr. 47. He testified that the onset of petitioner's stroke was consistent with the case reports described in Thoon and in Lin, where neurological deficits associated with stroke were found within 24 hours after administration of the influenza vaccination. *See* Pet. Ex. 26 & 27. In Thoon, the 10-year old girl developed blurred vision, a headache, and new-onset vertiginous giddiness one day after receiving the flu vaccine. Pet. Ex. 26 at 2. In Lin, the 75-year-old man developed "neurological deficit" seven hours after administration of the influenza A/H1N1 vaccination. Pet. Ex. 27 at 2. Dr. Tornatore stated that in the present case, petitioner's malaise and headache, which began the same day of the vaccination were likely related to an increase in cytokine and chemokines,

consistent with the findings of the Christian article, but that petitioner's personality changes that occurred the following day could have been from the stroke. Tr. 48.

c. Respondent's experts' opinions on vaccine causation

1. Dr. Steven Messé, neurologist

Dr. Steven Messé, respondent's neurology expert, provided two expert reports and testified during the entitlement hearing. Resp. Ex. A; Resp. Ex. B. Dr. Messé agreed that petitioner suffered a posterior cerebral artery ischemic stroke. Resp. Ex. A at 4. However, he opined that petitioner's stroke was unrelated to the influenza vaccine because there was a lack of evidence for a pro-thrombotic state post vaccination, that cryptogenic or stroke of unknown cause is common, and that petitioner had risk factors for stroke including hypertension. Resp. Ex. A at 6-7.

Dr. Messé explained that 80 percent of ischemic strokes occur due to a vascular mechanism, which can be a "blockage that reduces blood flow or a ruptured blood vessel and hemorrhage." Tr. 102. He stated that the "vast majority of strokes are related to atherosclerosis, or "hardening of the arteries," which occurs in the large or small arteries. Resp. Ex. A at 4; Tr. 103. Dr. Messe stated that approximately 20-25% of strokes are caused by clots that form in the heart and that "[a]trial fibrillation is the most common arrhythmia that adults experience and one of the leading mechanisms of stroke." Resp. Ex. A at 4. He noted that there are cryptogenic strokes, which mean that "there was no clear cause identified after a thorough work-up," and that it is one of the "most common conclusions reported in stroke cases." *Id.* at 6; Tr. 104. Dr. Messé's opinion was that the influenza vaccine was not likely the cause of petitioner's stroke, but instead his "difficult to control hypertension and evidence of vascular disease," were more likely to have been the cause of the stroke. Tr. 107.

Dr. Messé opined that the influenza vaccine is protective against stroke and that it is associated with a reduced, not increased risk of stroke. Resp. Ex. A at 4; Tr. 104. He cited an article by Grau et al. which studied whether the flu vaccine reduces the odds of a stroke. Resp. Ex. A, Tab 2.[13] The authors stated that "acute and chronic infections may contribute to stroke risk," and that "During influenza epidemics, hospitalizations for stroke and cardiac disease increase." *Id.* at 1. Thus, the purpose of the study was to determine if the influenza vaccine is associated with a reduction of risk for stroke. *Id.* The authors noted that other case-control studies showed that acute influenza infection is a trigger factor for stroke and that the "influenza vaccine may protect from stroke by preventing infections with influenza viruses and superimposed bacterial infections." *Id.* at 5. Furthermore, the authors stated that "pro-coagulant mechanisms, fever, dehydration, and proteolytic lesions to the vessel wall are mechanisms that could increase the risk of ischemic and hemorrhagic stroke after infections." *Id.* The authors found that the "odds of ischemic stroke were reduced significantly and the odds of hemorrhagic stroke but not TIA tended to be reduced by recent influenza vaccination." *Id.* at 4. Dr. Messé asserted that this study, along with others, demonstrates that the influenza vaccine is preventative

[13] Armin J. Grau et al., *Influenza Vaccination Is Associated with a Reduced Risk of Stroke,* 36 Stroke 1501-1506 (2005). [Resp. Ex. A, Tab 2].

and protective against stroke, which would mean that if there was as an association between the vaccine and stroke, "it would be extremely rare and unlikely." Tr. 106.

Dr. Messé also referenced the Smeeth et al. article, which examined whether acute infection and vaccination increase the short-term risk of vascular events. Resp. Ex. A, Tab 5.[14] He acknowledged that vaccinations limit wild-influenza infection, which would be protective against stroke, but he also asserted that the Smeeth article shows that the vaccination is protective in the first few days to a month after vaccination. Tr. 106. Dr. Messé stated that the Smeeth article found "that stroke rates were actually reduced in the period immediately following vaccination, extending up to 28 days after, with incidence ratios ranging from 0.72 up to 0.88." *Id.* at 5. He stated that "if vaccination induced strokes in some, it is extremely unlikely that this protective effect would have been seen." *Id.* However, Dr. Messé acknowledged that it is difficult to say that it is "impossible" that a stroke would occur after vaccination. Tr. 108. He stated that it would have to be "extremely rare" for a person who is more susceptible to develop a stroke after vaccination because the Smeeth article demonstrates that the flu vaccine is protective against stroke in the "early period after vaccination." Tr. 109.

During the hearing, Dr. Messé further explained the Smeeth article compared the risk of stroke or heart attack after vaccination to the risk of these conditions after an infection and found that the risk of a stroke or heart attack after infection is higher compared to vaccination. Tr. 113. He stated that the authors found that "within the first three days of getting a vaccination, the risk of stroke incident ratio is almost 25 percent less." Tr. 114. Dr. Messé did not address the identification of 76 cases of stroke post-vaccination in the first three days after the influenza vaccination. Importantly, the authors of Smeeth found that there is transient increase in the risk of a vascular even after the first few days of infection. Resp. Ex. A, Tab 5 at 6. Furthermore, the authors hypothesized that the "small protective effect seen after vaccination may have been due to administration of vaccination when people were in periods of relatively good health." *Id.* at 7. On re-direct examination, Dr. Messé conceded that the "protective finding" the authors of Smeeth identify is not that the flu vaccine itself reduces stroke and agreed with Dr. Tornatore that the flu vaccine "is not necessarily protective in the short-term." Tr. 145. He stated that he interpreted the article to show that it was not harmful and that there was no "increases of stroke in 20,000" people who received the flu vaccine. *Id.* He testified, "And so that, to me, is very reassuring, and if, it is a risk factor, it is extremely rare and unlikely." *Id.*

Dr. Messé opined that Dr. Tornatore's theory of how the influenza vaccine can cause an inflammatory response leading to a pro-thrombotic state that causes stroke lacks quality evidence and is "unlikely." Resp. Ex. A at 7; Tr. 119. More specifically, Dr. Messé stated that the influenza vaccine does not generate an inflammatory response "remotely similar to what you get from a wild-type infection," and, therefore, it is extremely unlikely that the vaccine could lead to a stroke. Tr. 119. He explained that the response to the vaccine, in his opinion, is a "less broad," and "less intense" response from a vaccination compared to a wild-infection. Tr. 120. Dr. Messé testified that if it were the case that the influenza vaccine could cause a stroke, he would "expect to see it" more because the influenza vaccine is being administered to the people at the highest risk of stroke. *Id.*

[14] Liam Smeeth, et al., *Risk of Myocardial Infarction and Stroke after Acute Infection or Vaccination*, 351 N. Engl. J. Med. 2611-2618 (2004). [Resp. Ex. A, Tab 5].

Dr. Messé agreed that all vaccines could cause neuroinflammatory diseases. Tr. 135. He testified that he believes that there is a "weak association" between the flu vaccine and Guillain-Barre syndrome ("GBS"), a neuroinflammatory disease, and that there is "some evidence" that the COVID vaccines that use the adenovirus "can probably increase the risk of GBS," and "very rarely cause clotting events." Tr. 135.

Turning to Dr. Tornatore's theory of how the flu vaccine could cause a stroke, Dr. Messé agreed that inflammation can contribute to the risk of clotting events occurring. Tr. 120. He reiterated that "there is increased risk of stroke if you develop the flu," but that "there is evidence for….stroke being less after vaccination." Tr. 121. However, he argued that "there is no evidence to suggest that such a pro-thrombotic state occurs after vaccination," and if such a state occurred after vaccination, "[one] would expect to see an association between vaccination and other thrombotic events." Resp. Ex. A at 6; Tr. 122. Dr. Messé noted that the Vickers et al. article did not show an increased risk for venous thromboembolism in the 1 to 10 days following flu vaccination. Resp. Ex. C, Tab 11 at 5.[15] The authors noted that known increased risk factors for venous thromboembolism include hypertension and metabolic disorders. *Id.* at 1. Further, they explained that "research has indicated that there is also a higher risk of VTE following influenza-like illness," and that the mechanism for VTE after infection was due to endothelial inflammation." *Id.* Vickers observed that the "[i]nfluenza vaccination has been shown to cause a transient increase in pro-inflammatory cytokine production," and that is why they sought to study the risk of VTE following influenza vaccination." *Id.* Dr. Messé testified that the Vickers article did not find any clotting event post-vaccination. Tr. 122.

Dr. Messé opined that petitioner's stroke was more likely caused by his pre-existing hypertension. Tr. 127; Resp. Ex. A at 6. He stated that petitioner required multiple drugs to control his hypertension and that he had "evidence of end-organ injury," which is "suggestive of pre-existing atherosclerosis." Resp. Ex. A at 6. Dr. Messé also stated that petitioner's MRI showed evidence of central nervous injury from ischemia which means that petitioner had prior vascular disease. Tr. 127. However, he acknowledged that the MRI finding is a common finding on MRIs in older adults, particularly ones with high blood pressure. Tr. 128.

Dr. Messé also opined that the atrial fibrillation that was found on petitioner's loop recorder a year and half later could have also been the cause of petitioner's stroke. Tr. 130. However, he testified, "Whether or not it caused the stroke that we are talking about today, I don't know. I certainly wouldn't say that's definitely the answer, but I also think it's definitely possible." Tr. 130. He explained that "intermittent Afib causing stroke" is much more likely than the vaccination causing petitioner's stroke. *Id.* He noted that one of petitioner's doctors associated petitioner's stroke to atrial fibrillation, albeit five years after the stroke. *Id.*; *see also* Pet. Ex. 34 at 29 ("Left PCA stroke most likely secondary to atrial fibrillation on chronic warfarin status post loop recorder placement with residual superior right quadrant anopia and cognitive changes."). However, Dr. Messé also conceded that while petitioner was initially hospitalized for his stroke, the treating physicians did not find evidence of atrial fibrillation. Tr. 147. He explained that sometimes patients present with atrial fibrillation and stroke, but in other

[15] Elizabeth R. Vickers, et al., *Risk of Venous Thromboembolism Following Influenza Vaccination in Adults aged 50 years and older in the Vaccine Safety Datalink*, 35 Vaccine 5872-5877 (2017). [Resp. Ex. C, Tab 11].

patients the atrial fibrillation is found later in time. *Id.* The finding of atrial fibrillation even a year after a stroke "is a very reasonable thing to say that probably caused [the] stroke." *Id.*

Dr. Messé testified that in petitioner's case, there are more alternative causes of his stroke, such as his pre-existing hypertension or later found atrial fibrillation, than evidence in support of vaccine causation. Tr. 148. It was his opinion that there is an association between the influenza infection and stroke, but that the influenza vaccine would not cause the same type of immune stimulus as a wild-infection such that it would lead to a stroke. *Id.*

2. Dr. Stephen Hedrick, immunologist

Respondent's immunology expert, Dr. Stephen Hedrick submitted one expert report and testified during the entitlement hearing. Resp. Ex. C. Dr. Henrick opined the immune response to the flu vaccine petitioner received does not elicit a systemic inflammatory response sufficient to elicit a blood coagulation response resulting in an ischemic event. Resp. Ex. C at 5. He testified "showing [vaccine] causation in this case is very difficult." Tr. 59.

Dr. Henrick stated that "there is strong evidence to support a causal relationship between an immune response to an infection leading to a cardiovascular event, but he disagreed that the immune responses to different antigens in the vaccine are equivalent or have the same physiological effects [as a wild-infection]. Resp. Ex. C at 2; Tr. 70-2. Dr. Henrick described the mechanism for how a viral infection can lead to blood clots as follows,

> …influenza A and influenza B, can directly induce the expression of Tissue Factor (TF), an inciting event leading to the cascade of coagulation…TF is constitutively expressed on cells that are physically separated from blood circulation. In the event of vascular damage, serum factors gain access to TF and the coagulation cascade begins. Alternatively, in the presence of inflammation, TF is expressed de novo on cells in contact with blood circulation. The basis for TF induction is most prominently the inflammatory cytokine known as Tumor Necrosis Factor (TNF) that is produced by many cells secondary to viral and bacterial infections.

Resp. Ex. C at 2; Tr. 65.

Dr. Hedrick testified that medical literature Dr. Tornatore relied upon to demonstrate that the flu vaccine could cause an increase in proinflammatory cytokines, does not actually show a significant enough increase in certain cytokines, such as TNF. Tr. 66-67. He testified that the Hingorani et al. article did not find a detectable increase in TNF. Tr. 65. Dr. Hedrick acknowledged that the Hingorani authors "did find an expected vascular effect," of the proinflammatory cytokines, but that the authors did not determine if there was any relevance to an ischemic event and that their conclusion was in the context to explain the association between infection and inflammation and the enhanced risk of acute cardiovascular event. Tr. 66. Dr. Hedrick also noted that the authors of Hingorani used a polysaccharide vaccine "that's known to cause inflammation at least on a low level," and that the typhoid vaccine is "very different from the split virus influenza vaccine that has not been shown to have the same effects." Tr. 68.

Dr. Hedrick asserted that the Christian article "did not actually demonstrate inflammatory markers comparable to what is seen in a wild-type infection," as asserted by Dr. Tornatore. Resp. Ex. C at 2; Tr. 69-70. In his report, Dr. Hedrick acknowledged that the Christian article did find a "small, but statistically significant difference in two inflammatory cytokines following receipt of the influenza vaccine," but that the authors "did not attempt to compare this to an actual influenza infection." Resp. Ex. C at 2; Tr. 70. Dr. Hedrick testified that the authors found a significant increase in migration inhibition factor (MIF), which is "an inflammatory factor" involved in the innate immune system. Tr. 69. However, he did not mention in his testimony that those who reported systemic symptoms also had an increase in TNF-α one day post-vaccination. *See* Pet. Ex. 50 at 5. He explained that his main point was that "you can't equate a very moderate, almost undetectable inflammatory response, with what you would see with an actual infection, which can be huge." Tr. 70. Although, he did concede that while there is a "significant correlation between stroke and an influenza infection," which is likely to be picked up in epidemiological studies, a "more mild elevation that could trigger a rare event, particularly in someone who is susceptible," is not eliminated. Tr. 71. Later in his testimony, Dr. Hedrick also conceded that there are a smaller number of adverse events associated with vaccination than with the wild infection and that sometimes those rare events are "small enough so that you can't even detect it in terms of looking at tens of thousands of patients." Tr. 78.

Dr. Hedrick stated, "…the magnitude of an immune response to an infectious agent is different than the magnitude of an immune response to a vaccine." Tr. 72. He stated that, "There is no doubt that the inflammatory response associated with the influenza virus infections differ both quantitatively and qualitatively from those elicited by a (semi) purified influenza vaccine. Resp. Ex C at 3. He wrote, "Many studies highlight the positive correlation between influenza and cardiovascular events, but I have not found a single study that showed an association between influenza vaccination and cardiovascular events. On the contrary, available studies show that influenza vaccination is protective." *Id.*; Tr. 73.

One of the many studies Dr. Hedrick referenced to support his opinion that the flu vaccine is protective against cardiovascular disease after a flu infection was the Behrouzi paper. Tr. 86; Resp. Ex. C, Tab 16.[16] The article reviewed other medical literature that examined the association between the flu, the flu vaccine and cardiovascular disease. Resp. Ex. C, Tab 16. The authors stated, "The latest meta-analysis of the cardioprotective effects of influenza vaccine found a 25% reduced risk of all-cause death." The articles provides that "heart disease has been the leading cause of the death in the U.S., with a 5% increase from 2019 to 2020 alone….Now, because of the Coronavirus Disease 2019 pandemic, it has never been more apparent to the public that there exists a vicious cycle between viral respiratory infections and cardiovascular disease." Resp. Ex. C, Tab 16 at 1. Furthermore, Behrouzi wrote, "[Viral respiratory infections] can create a systemic inflammatory environment that is conducive to major adverse cardiovascular events." *Id.* at 1-2. The authors noted that two recent studies found that "almost one in eight adult patients hospitalized with laboratory-confirmed influenza infection experienced an acute cardiovascular event," and that these patients had a median length of stay of 5 days in the hospital, a third required intensive care, and 7.3% died in the hospital. *Id.* at 2.

[16] Bahar Behrouzi & Jacob A. Udell, *Moving the Needle on Atherosclerotic Cardiovascular Disease and Heart Failure with Influenza Vaccine,* 23 Current Atherosclerosis Repts. https://doi/org/10.1007/s11883-021-00973-w (2021). [Resp. Ex. C, Tab 16].

The authors wrote, "Of those who died, 25% had an associated acute cardiovascular event, which may have been preventable had the initial influenza infection been averted." *Id.* Additionally, the authors stated that, "…several large meta-analyses of observational and trial data have shown that influenza vaccination is associated with a reduction in mortality and other adverse outcomes, including those of cardiovascular etiology, in adults with influenza infection." *Id.* at 4. Dr. Hedrick stated that the "whole point of this [study] was to give both practitioners and patients more evidence to support giving vaccines to patients at risk." Tr. 87.

Dr. Hedrick agreed that the flu vaccine is intended to elicit an immune response, however, the magnitude of the immune response to vaccine is "very, very different," than to the wild infection. Tr. 73. He explained that the infection from a virus expands and takes over a "good number of the cells of the epithelium of the lung and makes a huge number of cells and activates every possible mechanism of innate and adaptive immunity," which differs from the immune system's response to the vaccine which is, "limited to the injection site, for the most part. And while the inflammation could be felt systemically, it's much more of a limited stimulus." Tr. 74. Dr. Hedrick, referencing an article by Christiaansen et al., which examined the efficacy of vaccines to induce antigen-specific T-cells, asserted that it demonstrated that the proliferation of T-cells in the peripheral blood "does not compare to the proliferation and activation that [one] could get form an actual virus." Tr. 75; Resp. Ex. C, Tab 8.[17] Dr. Hedrick stated that the authors found that the vaccine patients were inoculated with caused a fivefold increase in peripheral blood T-cells and the vaccine with the adjuvant caused a nearly tenfold increase in peripheral blood T-cells. Tr. 75. When Dr. Hendrick was asked by the Court as to why the discussion of T-cells was relevant to Dr. Tornatore's theory of vaccine causation, he responded that the influenza vaccine is likely to produce a "T-cell recall response within hours," and that "T-cells are typically the cells that produce a large number of inflammatory cytokines." Tr. 77. He also testified that as for the body's innate immune response to the vaccine it is not the same as the innate immune response to an influenza infection, and that even if there was a rapid recall T-cell response coupled with an innate response to the vaccine, it would still be "moderate in the amount compared to an infection." Tr. 77-8. However, Dr. Hedrick conceded that the vaccine does stimulate a similar immune response to a vaccine, albeit at a "lower magnitude," to develop immune memory. Tr. 78. Additionally, Dr. Hedrick testified that "some of the same mechanisms are involved in vaccine-mediated immune activation compared to infection-mediated vaccination, but they are not equivalent." Tr. 89. He also agreed that a stroke after a wild flu infection is common enough to be found in epidemiological studies, but that does not eliminate the possibility that a more mild inflammatory elevation could trigger a rare event, particularly in someone who is susceptible. Tr. 71.

Dr. Hedrick also referenced the article by L'Huiller et al., which examined the T-cell response in organ transplant patients to a wild influenza infection or the flu vaccination, to support his opinion that the flu vaccine does not generate an inflammatory response as significant as the wild infection. Resp. Ex. C, Tab 9.[18] He stated that vaccines show a "very

[17] Allison F. Christiaansen et al., *CD11a and CD49d Enhance the Detection of Antigen-Specific T cells Following Human Vaccination,* 35 Vaccine 4255-4261 (2017). [Resp. Ex. C, Tab 8].

[18] Arnaud G. L'Huiller et al., *T-cell Response Following Natural Influenza Infection or Vaccination in Solid Organ Transplant Recipients,* 10 Nature 10104, https://doi.org/10.1038/s41598-020-67172-6. [Resp. Ex. C, Tab 9].

poor expansion and activation of a pathogen-specific T cell populations after vaccination," and that exposure to the wild infection "often results in an expansion of the virus-specific T-cell population on the order of 10,000-fold in a matter of days." Resp. Ex. C at 3. Dr. Hedrick testified that the article showed that there was almost "zero response" to the vaccine by the CD4 T-cells, which produce most of the inflammatory cytokines, and that the response to the H3N2 vaccine only produced a small amount of cytokines. Tr. 81. He interpreted L'Huiller to show that "the magnitude of the effect of inflammation in an infection is, in some cases, infinite over that which you get with the vaccination." Tr. 82. However, he conceded that the vaccine does produce "some" inflammatory response, but that it is "difficult to measure." *Id.* As Dr. Tornatore observed, the L'Huiller article also showed that in those who were vaccinated against the H3N2 component, the vaccine stimulated a similar pattern of elevation in IFNγ, TNFα, and IL-2 as did the wild infection albeit at a lower level. Tr 32; Resp. Ex. C, Tab 9 at 5.

Dr. Hedrick testified that Dr. Tornatore's theory of how the flu vaccine could cause a stroke was not supported by the medical literature. Tr. 59. He stated that Dr. Tornatore acknowledged that there is no medical literature that shows an increased incidence of stroke following the flu vaccination. *Id.* He testified that there is a stroke occurring every four minutes in the United States and that there are approximately 40 million doses of influenza vaccine given every year and thus, one could always find that a stroke occurs in proximity to the administration of a flu vaccination. Tr. 60. Dr. Hedrick stated that there has been "no trend….between influenza vaccine…and ischemic stroke." *Id.* He asserted that the Lin article, which is a case report of an older gentleman experiencing an ischemic stroke and an analysis of VAERS reporting of stroke post-vaccination, does not really demonstrate causation between the influenza vaccine and a stroke. Tr. 62. Instead, he argued that the paper only shows a very rare occurrence of strokes after flu vaccination and that it only demonstrates a temporal association between the flu vaccine and an ischemic event. *Id.* He stated that the paper demonstrates that "of the patients reporting an ischemic event, 18 percent occurred within the first 24 hours. So the timing is fine. There's no issue with the timing, but it doesn't show anything about causation." *Id.* Furthermore, Dr. Hedrick stated that the authors of Lin are "uncertain if an enhancement of the inflammatory immunological activity after vaccination is sufficient," to cause a symptomatic vascular occlusion. *Id.*

Similarly, Dr. Hedrick asserted that the Thoon article, a case report of child experiencing a stroke shortly after receiving the flu vaccine, only shows a temporal association between the vaccine and stroke. Tr. 63. He also stated that the authors of Thoon did not change their recommendation for all children to receive the seasonal flu vaccine. *Id.* When asked by the Court whether "there's a difference between saying that the data supports recommending vaccination for all people, because for most people…it's safe to receive, but [there] could still be a rare adverse event," Dr. Hedrick responded, "Yes," and that Thoon article does not specifically address that issue.

Dr. Hedrick testified that it was his opinion that the flu vaccine does not generate a sufficient systemic inflammatory response sufficient to result in a thrombotic event. Tr. 93. He stated that it was his opinion that the immune response to infection compared to vaccinations are "overwhelmingly different." Dr. Hedrick stated that there is no way to make a causal relationship between the flu vaccine and a stroke, given how commonly strokes occur and the

number vaccines administered. Tr. 92. On cross-examination, Dr. Hedrick appeared to concede that the seasonal flu vaccine can cause Guillain-Barre syndrome, a neuroinflammatory injury. Tr. 95.

III. Legal standard for entitlement

The Vaccine Act was established to compensate vaccine-related injuries and deaths. Section 10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" *Rooks v. Sec'y of Health & Hum. Servs.,* 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, reprinted in 1986 U.S.C.C.A.N. at 6287, 6344).

Petitioner's burden of proof is by a preponderance of the evidence. Section 13(a)(1). The preponderance standard requires a petitioner to demonstrate that it is more likely than not that the vaccine at issue caused the injury. *Moberly v. Sec'y of Health & Hum. Servs.,* 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Hum. Servs.,* 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, the petitioner must prove that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321 (quoting *Shyface v. Sec'y of Health & Hum. Servs*., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); *see also Pafford v. Sec'y of Health & Hum. Servs.*, 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner who satisfies this burden is entitled to compensation unless respondent can prove, by a preponderance of the evidence, that the vaccinee's injury is due to "factors unrelated to the administration of the vaccine." Section 13(a)(1)(B).

To receive compensation through the Program, petitioner must prove either (1) that he suffered a "Table Injury"— i.e., an injury listed on the Vaccine Injury Table— corresponding to a vaccine that she received, or (2) that he suffered an injury that was actually caused by a vaccination. See Sections 11(c)(1), 13(a)(1)(A); *Capizzano v. Sec'y of Health & Hum. Servs.,* 440 F.3d 1317, 1319-20 (Fed. Cir. 2006). Where as here, the petitioner does not allege a Table Injury, the petitioner must prove that the vaccine received actually caused the injury. To do so, the petitioner must establish, by preponderant evidence: (1) a medical theory causally connecting the vaccine and the injury ("*Althen* Prong One"); (2) a logical sequence of cause and effect showing that the vaccine was the reason for the injury ("*Althen* Prong Two"); and (3) a showing of a proximate temporal relationship between the vaccine and the injury ("*Althen* Prong Three"). Section 13(a)(1); *Althen*, 418 F.3d at 1278.

The causation theory must relate to the injury alleged. The petitioner must provide a sound and reliable medical or scientific explanation that pertains specifically to this case, although the explanation need only be "legally probable, not medically or scientifically certain." *Knudsen v. Sec'y of Health & Hum. Servs*., 35 F.3d 543, 548-49 (Fed. Cir. 1994). In *Kottenstette,* the Federal Circuit reiterated that proof of causation does not "require identification and proof of specific biological mechanisms[]" *Kottenstette v. Sec'y of Health & Hum. Servs.*, 861 Fed. Appx. 433, 441 (Fed. Cir. 2021) (citing *Knudsen*, 35 F.3d at 549). Causation "can be found in vaccine cases…. without detailed medical and scientific exposition of the biological

mechanisms." *Knudsen*, 35 F.3d at 549. It is not necessary for a petitioner to point to conclusive evidence in the medical literature linking the vaccine to the injury, as long as the petitioner can show by a preponderance of evidence that there is a causal relationship between the vaccine and the injury, whatever the details of the mechanism may be. *Moberly v. Sec'y of Health & Hum. Servs.*, 592 F.3d 1315, 1325 (Fed. Cir. 2010).

The petitioner cannot establish entitlement to compensation based solely on his assertions; rather, a vaccine claim must be supported either by medical records or by the opinion of a medical doctor. Section 13(a)(1). In determining whether the petitioner is entitled to compensation, the special master shall consider all material in the record, including "any . . . conclusion, [or] medical judgment . . . which is contained in the record regarding . . . causation." Section 13(b)(1)(A).

In Vaccine Act cases, expert testimony may be evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993); *see also Cedillo*, 617 F.3d at 1339 (citing *Terran v. Sec'y of Health & Hum. Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). In Vaccine Program cases, the *Daubert* analysis has been used in the weighing of the scientific evidence actually proffered and heard, rather than as a tool for the pre-trial exclusion of expert testimony. *Davis v. Sec'y of Health & Hum. Servs.*, 94 Fed. Cl. 53, 66–67 (Fed. Cl. 2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"), *aff'd*, 420 F. App'x 923 (Fed. Cir. 2011). The flexible use of the *Daubert* factors to determine the persuasiveness and/or reliability of expert testimony in Vaccine Program cases has routinely been upheld. *See, e.g., Snyder v. Sec'y of Health & Hum. Servs.*, 88 Fed. Cl. 706, 742–45 (2009).

Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Hum. Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe v. Sec'y of Health & Hum. Servs.*, 219 F.3d 1357, 1362 (Fed. Cir. 2000)). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 146 (1997)). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly*, 592 F.3d at 1325–26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Hum. Servs.*, 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

Close calls regarding causation must be resolved in favor of the petitioner. *Althen*, 418 F.3d at 1280 (holding that Congress created a system in which "close calls regarding causation are resolved in favor of injured claimants"); *Knudsen*, 35 F.3d at 551 ("If the evidence (on

alternative cause) is seen in equipoise, then the government has failed in its burden of persuasion and compensation must be awarded.").

IV. Discussion and application

a. *Althen* prong one

Under *Althen* prong one, petitioner must provide a "reputable medical theory," demonstrating that the vaccine received can cause the type of injury alleged. *Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1355-56 (Fed. Cir. 2006). Such a theory must only be "legally probable, not medically or scientifically certain." *Knudsen*, 35 F.3d 548-49. Petitioner may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009) (citing *Capizzano*, 440 F. 3d 1325-26). However, "[a] petitioner must provide a 'reputable medical or scientific explanation for [his] theory. While it does not require medical or scientific certainty, it must still be 'sound and reliable.' " *Boatmon v. Sec'y of Health & Human Servs.,* 941 F.3d 1351, 1359 (Fed. Cir. 2019) (quoting *Knudsen*, at 548-49).

Here, petitioner's expert, Dr. Tornatore proposed that the influenza vaccine induces an inflammatory response, leading to a pro-thrombotic state and an acute cerebral ischemic event. Pet. Brief at 17; Pet. Ex. 24 at 7. Dr. Tornatore supported his theory with several medical articles.

First, Dr. Tornatore observed that two articles describe case reports of strokes occurring in the first two days after flu vaccination. Tr. 16-18; Pet. Ex. 24 at 6-8; Pet. Exs. 26,27. The Thoon article, which described a case of a 10-year-old girl who developed a cerebellar stroke one day after receiving the flu vaccine. Pet. Ex. 26 at 2. The Thoon authors observed that the 10-year-old girl did not have MRA findings of cerebral angiopathy to explain the nature of her ischemic stroke, which had been seen on imaging of a four-year-old with an acute ischemic stroke following a wild influenza infection. *Id.* at 4. Dr. Tornatore testified that petitioner's infarct was in the same distribution as that of the 10-year-old girl described in Thoon. Tr. 17. Dr. Tornatore also noted that the 10-year-old did not have any underlying conditions that would put her at risk for a stroke. Tr. 17.

The other case report Dr. Tornatore referenced, Lin et al, described a 75-year-old-man who developed an ischemic stroke shortly after receiving the flu vaccine. Pet. Ex. 27 at 1. The authors of Lin noted that the patient developed neurological deficit approximately seven hours after vaccination. *Id.* at 2. Furthermore, Lin observed that the patient also had underlying stroke risk factors, such as hypertension, similar to petitioner's pre-existing hypertension. *Id.* In Lin, the authors also opined as to the cause of an ischemic event after vaccination, stating that "an inflammatory/immunological response after vaccination may trigger thrombosis superimposing a pre-existing prothrombotic state." *Id.* at 4. The authors stated that "the leading vaccine reported to be complicated with ischemic stroke is the seasonal flu vaccine," noting that 164 people reported having a stroke after administration of the seasonal flu vaccine in VAERS. *Id.* at 2. Furthermore, the authors explained that the VAERS data that they reviewed showed that of those

who suffered an ischemic stroke after a flu vaccine, 18% suffered the stroke in the first day after the vaccination. *Id.* at 4. They opined that the "rapid onset of symptomatic thrombosis may indicate a hypersensitive reaction in our patients." *Id.* Dr. Tornatore testified that the case reports by Lin and Thoon highlight rare events. Tr. 16. Lin also recognized the possible "underestimation of vascular complications after vaccination" in patients with multiple risk factors. Pet. Ex. 27 at 2. Dr. Tornatore stated, "If somebody has hypertension, diabetes, hyperlipidemia, then their blood vessels may be already more prone to a thrombotic event or ischemic event." Tr. 20.

While these two articles are case reports and do not establish vaccine causation by themselves, "case reports by their nature only present indicia of causation but that does not deprive them of all evidentiary weight." *Campbell v. Sec'y of Health & Human Servs.,* 97 Fed. Cl. 650 (Fed. Cl. 2011); *see also Coleman v. Sec'y of Health & Human Servs.,* No. 18-352V, 2021 WL 1291677 (Fed. Cl. Sec. Mstr. Feb. 16, 2021) ("While case reports cannot establish causation, they do provide some evidence of causation.").

However, Dr. Tornatore did not rely on case reports alone to support his theory that petitioner's stroke was caused by an inflammatory response to the influenza vaccine. The Christian article showed that the flu vaccine generates a transient pro-inflammatory response, as it is intended to do, which corresponds with subjective side effects. Pet. Ex. 50. The authors of Christian found that patients who reported common systemic side effects, such as a headache, fatigue, nausea, achiness, or mild fever, had significantly higher MIF, a pro-inflammatory cytokine, two-days post-vaccination and elevated TNF-α one day post-vaccination. *Id.* at 4-5. The authors stated that their study indicated that "subjective symptoms…correspond with inflammatory responses following influenza vaccination, as indicated by serum proinflammatory cytokine levels and body temperature." *Id.* at 6. Dr. Tornatore testified that petitioner experienced the type of systemic symptoms within 24-hours after the flu vaccine, which likely corresponded with a rise in inflammatory cytokines, as demonstrated by the Christian article. Tr. 29.

Then Dr. Tornatore persuasively explained how a transient inflammatory response to a vaccine could impair endothelial function in a susceptible individual, leading to a cardiovascular event by impairing vascular relaxation Pet. Ex. 48 at 2; Tr. 22. The Hingorani article lends significant support for Dr. Tornatore's opinion. In Hingorani, the authors tested "the hypothesis that a mild systemic inflammatory response (generated by the administration of a vaccine) impairs endothelium-dependent dilation in the arterial circulation." Pet. Ex. 49 at 1. The authors administered a polysaccharide typhoid vaccine and then tested plasma concentration of proinflammatory cytokines. *Id.* at 3. They found that the inflammatory cytokine IL-6 increased in the 8 hours after vaccination. The authors wrote, "…in relation to cardiovascular risk, the elevation of IL-6 is of particular interest because IL-6 is presumed to be an important, if not the principal stimulus to the synthesis of C-reactive protein, and elevated C-reactive protein seems to be predictive of risk of cardiovascular events." *Id.* at 3. While Hingorani did not find an increase in IL-1β, as observed by respondent's experts, they did find that the IL-1Ra (receptor antagonist), which is usually synthesized in response to the elevation of IL-1β, rose by 191% from baseline in the three hours after vaccination. *Id.* The authors explained that the increase in IL-1Ra suggests that "significant local cellular or tissue generation of cytokines can occur

without an increase in circulating concentrations. Therefore, we cannot exclude the possibility that the IL-1β and TNF-α were synthesized after vaccination." *Id.*

Furthermore, Hingorani found that intramuscular injection of the vaccine produced a "mild systemic inflammatory response in healthy volunteers that was associated with *profound,* but temporary, suppression of endothelium-dependent relaxation in forearm circulation" and that their findings "demonstrate that even a relatively mild systemic inflammatory response is associated with significant alteration in endothelial function of a type commonly thought to be associated with increased cardiovascular risk." *Id.* at 4. The study measured the effects of the vaccine on the production of bradykinin ("BK") and acetycholine ("Ach"), which measures the ability of the endothelium to generate vasodilation through the stimulation of nitric oxide in the vascular bed. Hingorani found that BK and ACh had decreased efficacy or potency in patients with a variety of cardiovascular disease, including hypertension, which was an indication of endothelial dysfunction. *Id.* When they tested BK and ACh potency post-vaccination, they found that BK was suppressed by almost 65% and the ACh response was also diminished. Similar suppression was not seen in non-vaccinated controls. *Id.* In the case of BK, the defect in endolthelium dependent relaxation had returned to baseline by 32 hours post-vaccination. *Id.* Hingorani explained "the endothelium is an important transducer of physical and chemical signals from the lumen of the vessel, and experiments in animals and in vitro suggest that changes reported here could alter vascular behavior to contribute to the disruption of tissue oxygenation, increased platelet and white cell adhesion to the vessel wall and predispose to vasospasm." *Id.* at 5. The transient suppression of BK may be particularly important because it plays a role in vascular homeostasis. *Id.* They concluded that "even a mild inflammatory reaction disturbs endothelial regulation of vascular tone in the arterial circulation." *Id.*

Dr. Tornatore testified that Hingorani used the vaccine-model to recreate what is seen with infection to demonstrate that changes in the vascular system were related to generation of inflammation and they demonstrated that the immune response to a vaccine can cause the same type of response as the wild infection. Tr. 24. Dr. Tornatore opined that in a susceptible individual with pre-existing vascular disease, like hypertension, the impairment of the endothelial relaxation of the blood vessels caused by the inflammatory response to the vaccine could cause a thrombotic stroke. Tr. 30; Pet. Ex. 48 at 2. He explained:

> …if somebody has underlying vascular disease, the inner lining of their blood vessel is not normal. They probably have some degree of artherosclerotic disease, there's already some embedded inflammation in the wall of the blood vessel, and then you add another inflammatory event on top of that with maybe some narrowing of the blood vessel, and then you'll get a thrombus formation in situ.

Tr. 30. The Hingorani paper substantially supports Dr. Tornatore's theory of vaccine causation. First, the authors found increased inflammatory cytokines hours of vaccination. *See* Pet. Ex. 49 at 2. Then the authors found an association between the mild increase in inflammation and profound suppression of endothelium-dependent relaxation in circulation. *Id.* at 3. Finally, the authors found that in those with pre-existing hypertension, the endothelial function was further impaired by the inflammation initiated by the vaccination, just as Dr. Tornatore opined. *Id.*; *see also* Tr. 30.

The respondent's experts, Dr. Hedrick and Dr. Messé disagreed with Dr. Tornatore's proposed mechanism, mainly arguing that the flu vaccine does not generate a sufficient inflammatory response to induce a "cascade of coagulation which could lead to a cardiovascular event, such as stroke," and that there is no epidemiological evidence that supports an increased risk of stroke post-vaccination. Resp. Ex. A at 7; Resp. Ex. C at 3. Drs. Hedrick and Messé argued that the medical literature supports an association between a wild influenza infection and an increased risk for a cardiovascular event, but there is no such association between the flu vaccine and stroke in epidemiological studies. Resp. Ex. B at 1-2; Resp. Ex. C at 2. They also recognized that it is the immune response to the infection, not the infection itself that increases the risk of the cascade of coagulation, that could lead to a stroke. *Id.* Dr. Hedrick explained in his report, "I acknowledge that there is strong evidence to support a causal relationship between immune responses elicited by virulent infectious agents and vascular coagulation that could potentially lead to a cardiovascular event." Resp. Ex. C at 2. However, he stated that the inflammatory response elicited by the vaccine is not equivalent to the inflammatory response to the wild infection and therefore, could not give rise to result in a thrombotic stroke. *Id.* at 4. Furthermore, both experts asserted that the flu vaccine is "protective" against stroke. Tr. 59,105.

There is no doubt that various studies filed in this case indicate that ischemic strokes are more common after the flu or other infections than after vaccination. *See* Resp. Ex. A, Tab 5 at 1. Further, these studies also indicate that the cause of the cardiovascular event is likely due to the robust immune response to the infection. *See* Resp. Ex. A, Tab 4 at 2 ("Influenza infection can activate systemic inflammatory responses and increase the sympathetic tone that plays a crucial role in the pathogenesis of atrial fibrillation.") *see also* Resp. Ex. C, Tab 15 at 1 ("Research has indicated that there is also a higher risk of venous thromboembolism…including pulmonary embolism following influenza-like illness."). Here, petitioner did not have the flu infection prior to his stroke. Instead, he was a susceptible individual with hypertension who received a flu vaccine, then experienced a stroke. The task of petitioner's expert, Dr. Tornatore, was to demonstrate a sound and reliable theory for which the flu vaccine could cause a stroke, which he did.

Furthermore, petitioners are not required to demonstrate a specific biologic mechanism that caused their disease, nor are they required to present medical literature or epidemiological studies in support of their theory. *See Kottenstette v. Sec'y of Health & Human Serv.*, 861 Fed. Appx. 433 (Fed. Cir. 2021) (citing *Knudsen*, 35 F.3d at 548-49)(reaffirming the principle that "proof of causation does not 'require identification and proof of a specific biological mechanism[.]'" *Andreu*, 569 F.3d at 1378-79. However, a petitioner's prong one theory must be sound and reliable. *See Boatmon v. Sec'y of Health & Human Servs.*, 941 F.3d 1351, 1359 (Fed. Cir. 2019). The lack of epidemiological studies to demonstrate an association between the flu vaccine and stroke is not necessary for petitioner to prevail on *Althen* prong one, and the lack of epidemiological studies did not persuasively rebut petitioner's theory. Additionally, the articles cited by respondent's experts did not find that there were no incidences of stroke after the flu vaccine, but only that there was not an increased risk *compared to a wild infection*.

The Smeeth article, filed by respondent, identified 76 cases of stroke occurring 1–3-day post-influenza vaccination. Resp. Ex. A, Tab 5 at 6. Furthermore, Smeeth stated that

intermittent changes to inflammation "may be linked to an increase in the risk of vascular events." Resp. Ex. A, Tab 5 at 1. The authors opined that inflammation may affect endothelial dysfunction, leading to a cardiovascular event. *Id.* Even though the authors concluded that there did not appear to be "a detectable increase in the risk of vascular events" after vaccination, they also endorsed Dr. Tornatore's theory stating that the vaccination can cause "mild transient inflammation and associated suppression of endothelium-dependent relaxation." *Id.* at 7-8. Furthermore, when asked by the Court if the epidemiological studies eliminate the possibility that a "more mild elevation in inflammation could trigger a rare event, particularly in someone who is susceptible," Dr. Hedrick conceded the epidemiological studies could not fully eliminate a rare event. Tr. 71. Thus, the risk of a stroke occurring after a wild infection may be greater in the wake of a wild flu infection than after the influenza vaccine, but this does not mean that that a rare event, such as the present case cannot occur.

In summary, Dr. Tornatore's theory is supported by the medical literature filed by both petitioner and respondent in this case. I find that petitioner has demonstrated a sound and reliable medically theory to explain how the flu vaccine can cause a stroke. Accordingly, the requirements of *Althen* prong one have been satisfied.

b. *Althen* prong three: temporal association

Althen prong three contains two parts: first petitioners must establish the "timeframe for which it is medically acceptable to infer causation," and second, they must demonstrate that the onset of the disease occurred in this period. *Shapiro v. Sec'y of Health & Human Servs.,* 101 Fed. Cl. 532, 542-43 (2011), *recons. denied after remand on other grounds,* 105 Fed. Cl. 353 (2012), *aff'd without op*., 503 F.App'x 952 (Fed. Cir. 2013).

Although a temporal association alone is insufficient to establish causation, under the third prong of *Althen*, a petitioner must show that the timing of the injury fits with the causal theory. *See Althen*, 418 F.3d. at 1278. The special master cannot infer causation from temporal proximity alone. *Thibaudeau v. Sec'y of Health & Human Servs.,* 24 Cl. Ct. 400, 403-04 (1991); *see also Grant v. Sec'y of Health & Human Servs.,* 956 F.2d 1144 (Fed. Cir. 1992) ("[T]he inoculation is not the cause of every event that occurs within the ten[-]day period…[w]ithout more, this proximate temporal relationship will not support a finding of causation." (quoting *Hasler v. U.S.*, 718 F.2d 202, 205 (6th Cir. 1983)).

Petitioner's stroke symptoms began one day after receiving the flu vaccine. Petitioner's medical records and his affidavits consistently reflect this window of onset. *See* Pet. Ex. 10 at 16-18. Petitioner reported feeling poorly since receiving the flu vaccine two days before going to the hospital, reflecting the initial inflammatory response to the vaccine described in Christian. *See* Pet. Aff. ¶ 7. Then he began to develop personality changes, which Dr. Tornatore explained were likely early symptoms of the stroke. Tr. 47. By Sunday, two days after vaccination, petitioner developed more evident physical symptoms, that caused a nurse at his congregation to recognize that he was having a stroke and called an ambulance. Pet. Aff. ¶ 10. Dr. Hoerst, a treating neurologist, also summarized petitioner's history, writing, "…yesterday, the patient had a drastic, acute change in personality. This persisted today, but while he was at work, he additionally developed some vision changes and noted that he was bumping into things," and

that she suspected that "some degree of his stroke began yesterday with his acute personality change as this was clearly a significant change noted by the wife." *Id.* at 36-37.

Dr. Tornatore opined that onset of stroke symptoms 24-hours after vaccination is appropriate due to an inflammatory response to the flu vaccine. Pet. Ex. 24 at 7; Tr. 47. Dr. Tornatore stated that petitioner's symptoms began one day after the vaccination, which manifested as a change in personality and irritability. Tr. 47. He testified that the Talaat article, along with the Christian article show that cytokines and chemokines can be activated "well-within seven hours post-vaccination" and that the Hingorani article shows that mild inflammation can lead to a change in vascular tone within a day of vaccination. Tr. 48; *see* Pet. Ex. 24 at 7;Pet. Ex. 48 at 4; *see also* Pet. Ex. 50 (finding an association between increased cytokines such as TNF-α and MIF one- and two-day post-vaccination and reporting of subjective side effects of vaccination); and Resp. Ex. C, Tab 10 (finding that certain cytokine increases occurred within 24 hours after influenza vaccination, and one patient had a "distinctively robust change in IL-6, IL-2, IL-8, IP-10, and MCP-1 in response to the influenza vaccination at 3 and 7 hours" post-vaccination.). All of these are reviewed in conjunction with the recognition of vasosupression within hours when the effects of a vaccine were measured on the vasculature of healthy volunteers by Hingorani.

Furthermore, the onset of petitioner's symptoms, beginning one day post-vaccination was consistent with the case reports Dr. Tornatore referenced. The Lin article described the case of a 75-year-old male who received the flu vaccine in the morning and began to experience neurological deficits approximately seven hours later. Pet. Ex. 27 at 2. The authors noted that their patient had other stroke risk factors, including hypertension, however, they opined that the vaccine may promote a pre-existing prothrombotic condition, which could lead to a stroke. *Id.* at 4. After reviewing the VAERS data, Lin observed that 18% of reported ischemic strokes after the seasonal flu vaccine occurred one day post-vaccination. *Id.* at 4. The Thoon article described a case of a 10-year-old developing a cerebellar stroke one day after receiving the seasonal flu vaccine. Pet. Ex. 26 at 2. Thoon explained that the 10-year-old developed acute onset "vertiginous giddiness, blurred vision, headache, and non-bilious vomiting," approximately one-day after receiving the flu vaccine. *Id.* The girl's MRI showed two areas of restricted diffusion in the left cerebellar hemisphere. *Id.* at 2.

Dr. Hedrick testified that onset of stroke either 24-48 hours after vaccination is problematic because "[t]here is a stroke occurring in the United States every four minutes," and with 40 million doses of the influenza vaccine administered every year, "you will always find something that common….in proximity." Tr. 60. Dr. Messe testified that there is not any "temporal association" between vaccination and "major clotting events," such as "heart attack, stroke, venous thromboembolism." Tr. 122.

Both Drs. Hedrick and Messe's opinions regarding *Althen* prong three are based on their general disagreement about Dr. Tornatore's theory that the flu vaccine can generate a sufficiently significant inflammatory response that results in a prothrombotic state, leading to a stroke. Relying on the Smeeth article, Dr. Messé stated that "stroke rates were actually reduced in the period immediately following vaccination, extending up to 28 days after," when compared to incidences of stroke after the confirmed diagnosis of an upper respiratory infection. Resp. Ex. A

at 5. However, the Smeeth article still did identify 76 cases of stroke occurring 1-3 days after the flu vaccine was administered and the authors also explained that "[t]he small protective effect seen after vaccination may have been due to the administration of vaccination when people were in periods of relatively good health." Resp. Ex. A, Tab 5 at 5-6. Furthermore, even if the authors did not find a statistically detectable increase in the risk of a vascular event post-vaccination, the authors still identified 76 cases of stroke occurring in the short time-period Dr. Tornatore stated was a medically acceptable timeframe for a stroke to occur post-vaccination.

Additionally, the Talaat article, filed by respondent, showed that there is an increase in inflammatory cytokine activity as early as three hours post-influenza vaccination. Resp. Ex. C, Tab 10 at 1. The authors found that IFN-γ and IP-10, which are inflammatory cytokines, "were significantly elevated 7 hours after vaccination," and remained elevated between 16 and 24 hours after administration. *Id.* One subject, who reported moderate myalgias and injection site pain after vaccination, "displayed a distinctive, early cytokine response profile which included IL-6, IL-2, IL-8, IP-10, MCP-1, TNF-α, TARC and MCP-4." *Id.* Dr. Tornatore testified that *Talaat* shows that "there are individuals who have very brisk immune responses even within 7 or 8 hours, not unlike the response that the petitioner had, and that can lead to an acute injury…within a 24-hour period of time because of the chemokine/cytokine chemical network that develops." Tr. 45. He also reiterated that the Hingorani article, which showed how a moderate change in inflammation, can cause endothelial vasodilator dysfunction, leading to changes in vascular tone within a day, which could result in a stroke. Tr. 48.

Based on the medical literature filed by petitioner and respondent, in conjunction with Dr. Tornatore's opinion, I find that an onset of 24-hours post-vaccination is a medically acceptable timeframe to infer causation. Dr. Tornatore provided persuasive testimony, supported by medical literature, to show how the flu-vaccine can cause a rapid and substantial cytokine inflammatory response, which can result in changes to endothelial function. He demonstrated that especially in a susceptible individual this can lead to a stroke. Although the *Smeeth* article, along with other articles, assert that the risk is greater for individuals to develop a stroke after a wild infection, these articles still identified cases of stroke occurring within 24-hours after vaccination, even if the risk was classified as "not statistically significant." Finally, Dr. Hedrick conceded that the epidemiological studies which found a correlation between the flu infection and stroke, do not eliminate the possibility that a mild elevation of inflammation triggered by the flu vaccine may result in a rare event, particularly in a susceptible individual. Tr. 71. As such, petitioner has satisfied the third *Althen* prong.

c. *Althen* prong two: logical sequence of cause and effect

Under *Althen* prong two, a petitioner must prove by a preponderance of the evidence that there is a "logical sequence of cause and effect showing that vaccination was the reason for the injury." *Capizzano,* 440 F.3d at 1324 (quoting *Althen,* 418 F.3d at 1278). The sequence of cause and effect must be "'logical' and legally probable, not medically or scientifically certain." *Althen,* 418 F.3d at 1278. The petitioner need not make a specific type of evidentiary showing, i.e., "epidemiologic studies, rechallenge, the presence of pathological markers or genetic predisposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." *Capizzano,* 440 F.3d at 1325. Instead, petitioner may

satisfy his burden by presenting circumstantial evidence and reliable medical opinions. *Id.* at 1325-26.

With respect to *Althen* prong two, I find that petitioner has provided preponderant evidence that the November 7, 2014 flu vaccination caused his stroke. This finding is based on the petitioner's medical records, the statements of petitioner and his wife's, Dr. Tornatore's expert opinion, and the biological mechanisms described by Hingorani, Christian and Talaat.

Petitioner's medical records establish that prior to receiving the flu vaccine, he had hypertension, but he was taking Lisinopril and Ziac to control it. Pet. Ex. 10 at 4. Through affidavits, petitioner stated that the same day he received the flu shot, he began to feel sick and went to bed early. Pet. Aff. ¶ ¶ 6-7; Pet. Ex. 23 at ¶ 9. Petitioner stated that the next day, when they went to visit his wife's cousin outside of Philadelphia, Pennsylvania, he still felt sick and spent most of the visit resting. Pet. Aff. ¶ 8. His wife described significant personality changes in him later in the day. On November 9, 2014, two days after the vaccination, while at his church helping to prepare for service, he began to have difficulty controlling his body movements and keeping his balance. Pet. Aff. ¶ 10. An ambulance was called for him and it took him to the emergency department of Reading Hospital. While in the hospital, petitioner reported that he was ill the day before and that he had received a flu shot on Friday. Pet. Ex. 10 at 11.

Petitioner's primary symptoms were a headache, dizziness, and visual changes. Pet. Ex. 10 at 11. Petitioner had an echocardiogram in the emergency department which showed, "normal sinus rhythm at 68 beats per minute," and there was "normal intervals, no acute ST elevations nor ST segment depressions." *Id.* at 18. When Dr. Karen Hoerst, neurologist, examined petitioner later that day, she wrote that petitioner was a 62-year-old male with a "history of hypertension who presented to the emergency department with vague complaints of feeling unwell x 1 day. He reports that he did not feel like himself. Then today, developed headache, feeling of dizziness but not vertigo, and possible right sided visual changes….Speaking to his wife, she notes that yesterday, the patient had a drastic, acute change in personality (typically a kind and gentle person, he became angry and very short with her, which she reports she has never before seen, even if he is not feeling well)….His CT showed early edema in the left occipital lobe. Given the acute personality change since yesterday with progressive symptoms in conjunction with the CT findings, he was not given IVTPA. He underwent stat MRI/MRA imaging. He was found to have a left PCA infarct." *Id.* at 34-35. Her assessment was that petitioner had a PCA stroke which appears large vessel in etiology. *Id.* at 37. Additionally, she stated that she "suspect[ed] that some degree of his stroke began yesterday with his acute personality change as this was clearly a significant change noted by his wife." *Id.*

Petitioner had a follow-up with Dr. Hoerst on January 19, 2015. Pet. Ex. 9 at 4. At this appointment, she indicated that petitioner had undergone a transesophageal echocardiogram while in the hospital, which showed "no evidence of arrhythmia." *Id.* She did recommend that petitioner be evaluated by a cardiologist for placement of an implantable loop recorder to "look for underlying occult atrial fibrillation." *Id.* After the physical examination, she wrote that petitioner had a "left PCA infarct of unclear etiology," and that "certainly hypertension is a risk factor for stroke, but given that the remainder of his intracranial vasculature overall looks good, I

think we must evaluate him for other etiologies of stroke." *Id.* at 6. Dr. Hoerst repeated her recommendation for a loop recorder. *Id.*

Petitioner had a loop recorder placed on April 10, 2015. Pet. Ex. 5 at 7-8. On August 22, 2015, petitioner was admitted to Reading Hospital after his wife found him laying down, unresponsive. Pet. Ex. 10 at 168. Petitioner was diagnosed with a "new onset seizure, likely secondary to left PCA stroke." *Id.* at 156. Furthermore, it was noted that petitioner's hypertension was "well controlled on….Norvasc, Ziac, and lisinopril." *Id.* A brain MRI taken on August 23, 2015 showed a "chronic left PCA distribution infarct," but no change. *Id.* at 160. Petitioner was discharged to acute rehabilitation until August 31, 2015. *See* Pet. Ex. 10 at 281. All of the experts agreed that he likely suffered a seizure secondary to his original stroke at this time. Tr. 43, 129.

On October 15, 2015, at a follow-up cardiology appointment, the loop recorder showed "three symptom episodes and one tachycardia episode." Pet. Ex. 5 at 10. The tachycardia event was interpreted as "noise," but that the first symptom episode was a single "PAC," and that the "second symptom episode showed two single PACs and the third was negative for arrhythmia or extra beats." *Id.* The Impression was "cryptogenic stroke, status post loop recorder with no evidence of arrhythmias. He was originally maintained on a full-dose aspirin. He had a recent DVT and PE. We will have him drop down to 81 mg now that he is fully anticoagulated on Coumadin." *Id.*

Petitioner had a follow-up appointment with neurologist, Dr. Hoerst on October 19, 2015. Pet. Ex. 9 at 12-13. Under Chief Complaint it noted that the appointment was for a "follow-up left PCA infarct, presumed embolic stroke of unknown source." Pet. Ex. 9 at 12. Dr. Hoerst wrote that "petitioner was admitted to the hospital in September after being found unresponsive, postiical from a [p]resumed seizure….He has not had any seizures or events since hospitalization." *Id.* at 13. Dr. Hoerst's impression was, "63-year-old-man who had a left PCA infarct in November of 2014, with a prior history of hypertension, but no definitive etiology to his large vessel stroke, now complicated by presumed seizure." *Id.*

I do not find Dr. Messé and Dr. Hedrick's opinions that petitioner's stroke was caused by his underlying hypertension or much later diagnosed atrial fibrillation persuasive. First, Dr. Messe acknowledged in his first report that it would be "difficult to conclude with confidence that [the atrial fibrillation] was the proximate cause of [petitioner's] stroke," because of the "duration of time between the stroke and identification of the atrial fibrillation." Resp. Ex. A at 6-7. Further, Dr. Tornatore explained that at the time of the stroke, petitioner did not demonstrate atrial fibrillation and it was only identified on his loop recorder in September 2016, nearly two years after the stroke. *See* Pet. Ex. 30 at 5.

Additionally, prior to the onset of petitioner's stroke, the medical records demonstrate that petitioner was experiencing systemic symptoms in response to the vaccination, including fatigue, nausea, and upset stomach. *See* Pet. Ex. 10 at 16 ("He has been feeling somewhat poorly since receiving a flu vaccine about 2 days ago. Generalized malaise, and irritability."); *see also* Pet. Aff. at ¶ 7-8. The symptoms the petitioner reported to medical professionals and described in his affidavit are classified as "systemic symptoms" to the flu vaccine as described in the

Christian article. *See* Pet. Ex. 50 at 1. Dr. Tornatore testified that the symptoms petitioner described were evidence that he was having an immune response to the vaccine and that the reason for his symptoms were because of the production of inflammatory chemokines and cytokines. Tr. 29.

Dr. Tornatore acknowledged that petitioner was likely a susceptible individual, with pre-existing hypertension, being controlled with medication. Tr. 45; Pet. Ex. 48 at 2. He testified that hypertension is associated with endothelial dysfunction. Tr. 45-46. Furthermore, he testified endothelial dysfunction may be triggered by inflammation, which would affect endothelium dependent dilation in arterial circulation. *Id.*; *see also* Pet. Ex. 49 at 1. Dr. Tornatore explained that petitioner's likely pre-existing inflammation in the blood vessel walls was exacerbated by the inflammation generated by the flu vaccine which could lead to a thrombus formation, resulting in a stroke one day post-vaccination. Tr. 46.

The mechanism explained by Dr. Tornatore, and supported by Hingorani, Christian, and Talaat, also lend support to a finding of a logical sequence of cause and effect. As noted above, petitioner initially described the more common inflammatory type symptoms described in Christian within the early hours after the vaccination. The following day petitioner began to develop symptoms that Dr. Tornatore and Dr. Hoerst believe were more likely secondary to the stroke, and then on the second day he demonstrated significant signs and symptoms that led to his hospitalization and the diagnosis of an MRI confirmed, posterior cerebral artery stroke. Tr. 47. This evolution of initially more general inflammatory symptoms, to stroke symptoms affecting the posterior cerebrum more distinctly in the territory supplied by the PCA, appears to be quite consistent with the underlying mechanism described by Hingorani and endorsed by Dr. Tornatore. As Dr. Tornatore testified, Hingorani demonstrated that a transient increase in inflammatory cytokines after a vaccination caused a profound reduction in the vasodilator mechanisms in the vasculature leading to vasospasm or thrombus formation. *See* Pet. Ex. 49. Additionally, Dr. Tornatore pointed to the variability in immune response between different people and to the potential for a stronger immune response than average as occurred in the super responder in Talaat. Resp. Ex. C, Tab 10 at 1. While it is not necessary to conclude that petitioner was a super responder to the vaccine, the variability in immune response occurs along a spectrum and he may well have had a greater than average response.

Dr. Hedrick essentially proposed a theory of coincidence when he pointed to the frequency of strokes and vaccination in the population at large to negate vaccine causation. However, "the Vaccine Act does not require the petitioner to bear the burden of eliminating alternative causes where the other evidence on causation is sufficient to establish a prima facie case." *de Bazan v. Sec'y of Health of Human Servs.,* 485 F.3d 1146, 1150 (Fed. Cir. 2007). Additionally, petitioners do not bear a burden to "discount *every* potential cause that exists within the entire realm of possibility." *Pafford v. Sec'y of Health & Human Servs.*,64 Fed. Cl. 19, 35 (2005), *aff'd* 451 F.3d 1352 (Fed. Cir. 2006). Here, petitioner has demonstrated a sound and reliable theory to explain how the flu vaccine could cause a stroke. Further, petitioner's medical course was also consistent the case reports described in Thoon and Lin, where stroke symptoms began one-day after vaccination. Additionally, the Smeeth article filed by the respondent also found that 18% of reported strokes occurred within one day of vaccination. Resp. Ex. A, Tab 5; Tr. 62. While the literature indicates that strokes occur more often after a

wild flu infection, that statistic does not overcome the logical explanation for a less frequent adverse event after receipt of the flu vaccine that has been presented in this case. Finally, respondent's expert, Dr. Hedrick conceded that the epidemiological studies filed in this case would not identify a case where mild inflammation would trigger a rare cardiovascular event, particular in someone is who susceptible, as was the petitioner. *See* Tr. 71.

When a petitioner has established that vaccination can cause a given condition and has demonstrated that the timing prong has been met, it allows the petitioner to establish that vaccination was the but-for cause of his condition. *Cobb v. Sec'y of Health & Human Servs.*, No. 17-1123V, 2023 WL 6457568, at * 24. "Evidence demonstrating petitioner's injury occurred within a medically acceptable time frame bolsters a link between the injury alleged and the vaccination at issue under the "but-for" prong of the causation analysis." *Capizzano,* 440 F.3d at 1326 (finding medical opinions that explain how a vaccine can cause the injury alleged coupled with evidence demonstrating a close temporal relationship "are quite probative" in proving actual causation.); *Pafford,* 451 F.3d at 1358; *see also Contreras,* 107 Fed. Cl. at 295 (finding that there is a "logical overlap between the three *Althen* prongs, and that evidence that goes to one prong may also be probative for another prong.").

Here petitioner has demonstrated that his course after receiving the flu shot on November 7, 2014 was consistent with the theory proposed by Dr. Tornatore and there was not sufficient evidence in the record to establish an alternative cause to petitioner's stroke. Thus, petitioner has demonstrated by preponderant evidence *Althen* prong two.

V. Conclusion

Upon review of the evidence submitted in this matter, including the medical records, the experts' opinions, the medical literature, and the testimony, I conclude that petitioner has provided preponderant evidence in support of his claim that the flu vaccine caused him to develop a stroke shortly after his vaccination. Petitioner is therefore entitled to compensation under the Vaccine Act. A separate damages order will be issued.

IT IS SO ORDERED.

s/Thomas L. Gowen
Thomas L. Gowen
Special Master